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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/781,499	02/18/2004	Michel Chateau	34076/US	6087

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EXAMINER	
SHAHNAN SHAH, KHATOL S	
ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/781,499	CHATEAU ET AL.	
	Examiner	Art Unit	
	Khatol S. Shahnan-Shah	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2008 and 08 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11,13 and 22-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9, 11,13 and 22-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO AMENDMENT

1. Applicants' submission filed on 11/13/2008 has been entered. Claims 1, 2, 8 and 11 have been amended. Claims 10 and 12 have been canceled. New Claims 22-32 have been added. Claims 15-21 have been canceled by a previous amended.

2. Claims 1-9, 11, 13 and 22-32 are pending and under consideration.

Rejections Moot

3. Rejection of claims 10 and 12 under 35 U.S.C. 102 (b), made in paragraph 12 of office action mailed 1/18/2007 is moot in view of cancellation of said claims.

Rejections Maintained

4. Rejection of claims 1-4 and 8-9, 11, 13 and 14 under 35 U.S.C. 102 (b), made in paragraph 12 of office action mailed 1/18/2007 is maintained.

The rejection was stated below:

Claims 1-4 and 8-9, 11, 13 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakamori et al. (Applied Microbial Biotechnology, vol.52, pp. 179-185, 1999).

The claims are drawn to a method for the preparation of evolved microorganisms permitting a modification of metabolic pathways, comprising the following steps: a) preparing a modified microorganism by genetic modification of cells of an initial microorganism so as to inhibit the production or consumption of a metabolite when that microorganism is grown on a defined medium, thereby impairing the ability of that microorganism to grow; b) culturing the modified microorganism thereby obtained on said defined medium to cause it to evolve, where the defined medium can contain a co-substrate to allow such evolution; and c) selecting a modified microorganism able to grow on said defined medium, if necessary with a co-substrate.

Nakamori et al. teach a preparation of evolved microorganisms permitting a modification of metabolic pathways (see abstract). Nakamori et al. teach preparing a modified microorganism by genetic modification of cells of an initial microorganism so as to inhibit the production or consumption of a metabolite (methionine) when that microorganism is grown on a defined medium, see page 180 wherein E.coli JM 109 cells in the late exponential phase in LB medium were mutagenized. Nakamori et al. produced

L-methionine-analogue resistant mutants (see page 180). Nakamori et al. teach culturing the modified microorganism thereby obtained on said defined medium to cause it to evolve, where the defined medium can contain a co-substrate to allow such evolution and c) selecting a modified microorganism able to grow on said defined medium, if necessary with a co-substrate, see page 180 under selection and cultivation of L-methionine-producing mutants (i.e. an evolved microorganism). Nakamori et al teach biosynthesis pathway of amino acids and methionine (see title and abstract).

Nakamori et al. also teach limitation of claims 8-14 wherein the evolved microorganism possesses at least one evolved gene coding for an evolved protein (see page 182 Introduction of the wild-type metJ gene into the L- methionine-producing strain with a mutant metJ gene and page 183 Molecular modeling of the DNA-binding region in the mutant MetJ protein). The prior art anticipates the claimed invention.

Applicants' arguments filed 7/25/2008 have been fully considered but they are not persuasive.

Applicants argue:

- Nakamori Cannot Anticipate Because It Does Not Teach A Directed Genetic Modification Or The Inhibition Of The Production Or Consumption Of A Substrate

- The claims require generating a genetic modification in a gene of interest that inhibits the production or consumption of a metabolite by directed mutation. Nakamori, in contrast, uses random mutagenesis to generate hundreds of thousands (at least) of random mutagenic events. Nakamori then eventually identifies some cells in which an overexpressor phenotype of methionine is identified.

- Nakamori Teaches Against the Instant Invention As discussed above, the instant invention teaches a method of producing an evolved microorganism requiring, in part, the step of generating a microorganism wherein the production or consumption of a substrate is inhibited. In contrast, Nakamori explicitly states: "The construction of mutants that

have a genetically altered regulatory mechanism *is probably essential* for the fermentative production of L-methionine." Pg. 179, 2nd column, last sentence (emphasis added). This statement is made with regard to the repressor genes *metd and metK.*Thus, the *essential* requirement, as taught by Nakamori, is the removal of the negative feedback exerted by the *metal* gene. There is no evolution of a "compensatory metabolic pathway" as is required by the instant claims. Therefore, for this reason alone, the rejection is overcome and should be withdrawn. Applicants respectfully request same.

- *The* Process of Nakamori Does not Result in a Compensatory Metabolic Pathway As discussed above and as required by the claims, the instant invention discloses the genetic modification of a gene of interest wherein the production or consumption of a metabolite is inhibited such that a compensatory metabolic pathway is evolved. In Nakamori, there is no difference in the pathway responsible for methionine synthesis other than the negative feedback mechanism is eliminated. No new substrates are available to the organism for methionine synthesis and no compensatory pathways are necessary (or indeed ever evolved). In Nakamori, the wild type pathway continues to produce methionine using pre-mutagenic synthesis steps. Thus, because the instant claims require the debilitation of a biosynthesis pathway and the evolution of a compensatory pathway, Nakamori cannot anticipate the instant invention. For this reason alone, the rejection is overcome and should be withdrawn.

- *Nakamori* Teaches A Different Process Having Different Steps As amended herein, the present invention claims a method for preparing an evolved microorganism comprising the steps of: generating a directed genetic modification in a gene of interest in an initial microorganism to yield a modified microorganism wherein the production or consumption of a substrate is inhibited when the modified microorganism is grown on a

defined medium, impairing the ability of the modified microorganism to grow; b) culturing the modified microorganism obtained in step (a) on said defined medium, allowing the modified microorganism to evolve a compensatory metabolic pathway to compensate for the impaired growth, wherein the defined medium can contain a co-substrate promoting the evolution; and c) selecting an evolved microorganism from step (b) able to grow on said defined medium; wherein a compensatory metabolic pathway is evolved allowing the evolved microorganism to proliferate on the defined medium.

In response to applicants' arguments the office brings applicants attention to the instant specification (see page 3) following definitions:

Evolved microorganism as according to the invention an **'evolved microorganism' is defined as a microorganism obtained by selection of a modified microorganism**. The evolved microorganism displays at least one difference from the modified microorganism. This difference may, for example, be the improvement of an enzymatic characteristic, or the creation of a new metabolic pathway.
According to the invention a **'metabolic pathway'** is one or more enzymatic reactions the succession of which forms a molecule (product) that is different from the starting molecule (substrate).
According to the invention a **'modification'** is a change, in **particular a deletion**, of at least one gene and/or its promoter sequence, which gene codes for an enzyme.
According to the invention a **'metabolite'** is a molecule synthesized and/or transformed by the microorganism.

Page 6 further recites "According to the invention a 'modified microorganism' is a microorganism obtained by performing controlled modifications, i.e., that are not the result of a process of evolution. Examples of such a modification are the **directed mutation or deletion of a gene, or the directed modification of a promoter**.

Therefore, according to applicants own definitions Nakamori et al. do teach a preparation of evolved microorganisms by modifying a metabolic pathways (see abstract). Nakamori et al. teach preparing a **modified microorganism by genetic modification of**

cells of an initial microorganism so as to inhibit the production or consumption of a **metabolite** (methionine) when that microorganism is grown on a defined medium, see page 180 wherein E.coli JM 109 cells in the late exponential phase in LB medium were mutagenized. Nakamori et al. produced L-methionine-analogue resistant mutants (see page 180). Therefore, Nakamura's mutation does result in a specific mutation in metabolic pathway. Nakamori et al. do teach **Directed Genetic Modification** and **Modified Microorganism which is then Cultured.** Nakamori et al. teach preparing a modified microorganism by genetic modification of cells of an initial microorganism so as to inhibit the production or consumption of a metabolite (methionine) when that microorganism is grown on a defined medium, see page 180 wherein E.coli JM 109 cells in the late exponential phase in LB medium were mutagenized. Nakamori et al. produced L-methionine-analogue resistant mutants (see page 180). Nakamori et al. teach culturing the modified microorganism thereby obtained on said defined medium to cause it to evolve, where the defined medium can contain a co-substrate to allow such evolution and c) selecting a modified microorganism able to grow on said defined medium, if necessary with a co-substrate, see page 180 under selection and cultivation of L-methionine-producing mutants (i.e. an evolved microorganism).

5. Rejection of claims 1-7 under 35 U.S.C. 102 (b), made in paragraph 13 of office action mailed 1/18/2007 is maintained.

The rejection was as stated below:

Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 93/177112 published 2 September 1993.

The claims are drawn to a method for the preparation of evolved microorganisms permitting a modification of metabolic pathways, comprising the following steps: a) preparing a modified microorganism by genetic modification of cells of an initial microorganism so as to inhibit the production or consumption of a metabolite when that microorganism is grown on a defined medium, thereby impairing the ability of that microorganism to grow; b) culturing the modified microorganism thereby obtained on said defined medium to cause it to evolve, where the defined medium can contain a co-

substrate to allow such evolution; and c) selecting a modified microorganism able to grow on said defined medium, if necessary with a co-substrate.

WO 93/177112 teaches a preparation of evolved microorganisms permitting a modification of metabolic pathways i.e. biosynthesis pathway of amino acids (see abstract and amended claims). WO 93/177112 teaches preparing a modified microorganism by genetic modification of cells of an initial microorganism so as to inhibit the production or consumption of a metabolite (methionine) when that microorganism is grown on a defined medium (see claims). WO 93/177112 teaches preparing a modified microorganism by genetic modification of cells of an initial microorganism see amended claim 1. WO 93/177112 teaches culturing the modified microorganism thereby obtained on said defined medium to cause it to evolve, where the defined medium can contain a co-substrate to allow such evolution and c) selecting a modified microorganism able to grow on said defined medium, if necessary with a co-substrate, see claims specially claim 1. WO 93/177112 teaches limitations of claims 5-7 wherein the metabolic pathway consumes NADPH (see figure 1). WO 93/177112 teaches biosynthesis pathway of amino acids, methionine (see title and abstract). The prior art anticipates the claimed invention.

Applicants' arguments filed 7/25/2008 have been fully considered but they are not persuasive

Applicants argue:

- In contrast, Lievense describes a method for enhancing methionine production in a fermentation process by transforming a microorganism with a homoserine-activating enzyme gene and a sulphur-incorporating enzyme gene. The aim of these genetic modifications is to improve the production of methionine by over-expressing known genes~ supplied in trans, encoding for known enzymes involved in the biosynthesis pathways and deregulating the feedback mechanisms of those pathways. Pg. 6, second full paragraph. The process of Lievense does not teach a directed evolution process in which a "compensatory metabolic pathway" is induced in the microorganism but, rather, a process of identified genetic transformations. Further, applicants point out that Lievense does not teach

the use of a defined culture medium but a culture medium containing glucose, soy hydrolysate, and inorganic nutrients. As discussed in depth in the previous response, soy hydrolysate cannot comprise a defined medium. Soy
hydrolysate is a complex mixture of various soy components. The transformed cells of Lievense are not auxotrophic and would not be able to grow on a defined medium.

In response to applicants' arguments the office brings applicants attention to the instant specification (see page 3) following definitions:

evolved microorganism as according to the invention an **'evolved microorganism' is defined as a microorganism obtained by selection of a modified microorganism**. The evolved microorganism displays at least one difference from the modified microorganism. This difference may, for example, be the improvement of an enzymatic characteristic, or the creation of a new metabolic pathway.
According to the invention a **'metabolic pathway'** is one or more enzymatic reactions the succession of which forms a molecule (product) that is different from the starting molecule (substrate).
According to the invention a **'modification'** is a change, in **particular a deletion**, of at least one gene and/or its promoter sequence, which gene codes for an enzyme.
According to the invention a **'metabolite'** is a molecule synthesized and/or transformed by the microorganism.

Page 6 further recites, "According to the invention a 'modified microorganism' is a microorganism obtained by performing controlled modifications, i.e., that are not the result of a process of evolution. Examples of such a modification are the **directed mutation or deletion of a gene, or the directed modification of a promote**r.

Therefore, according to applicants own definitions WO 93/177112 teaches a preparation of evolved microorganisms permitting a **modification of metabolic pathways i.e. biosynthesis pathway of amino acids** (see abstract and amended claims). WO 93/177112 teaches preparing a **modified microorganism by genetic modification** of cells of an initial microorganism so as to inhibit the production or consumption of a

metabolite (methionine) when that microorganism is grown on a defined medium (see claims). As to applicants arguments that WO 93/177112 only teaches enhancement not inhibition.

In response applicants' attention is drawn to the language of the WO 93/177112 abstract "and/or by modifying the methionine biosynthetic pathway" when a reduced sulfur source is used in the medium production of methionine is enhanced and when an oxidized sulfur source is used production of methionine is inhibited (see table 1, page 7).

New Rejections

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 1, 2, 3, 8, 9, 11, 13, 14 and 22-32 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13-14 and 38-49 of copending Application No. 10/546,139. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of both applications are drawn to method of producing an evolved protein from an evolved microorganism comprising the same steps and material modifying a gene of interest in the organism to evolve a compensatory metabolic pathway to impair growth. .

This is a provisional obviousness-type double patenting rejection.

Claim Rejections - 35 USC § 102

8. Claims 22-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakamori et al. (Applied Microbial Biotechnology, vol.52, pp. 179-185, 1999).

Nakamori et al. teach a preparation of evolved microorganisms permitting a modification of metabolic pathways (see abstract). Nakamori et al. teach preparing a modified microorganism by genetic modification of cells of an initial microorganism so as to inhibit the production or consumption of a metabolite (methionine) when that microorganism is grown on a defined medium, see page 180 wherein E.coli JM 109 cells in the late exponential phase in LB medium were mutagenized. Nakamori et al. produced L-methionine-analogue resistant mutants (see page 180). Nakamori et al. teach culturing the modified microorganism thereby obtained on said defined medium to cause it to evolve, where the defined medium can contain a co-substrate to allow such evolution and c) selecting a modified microorganism able to grow on said defined medium, if necessary with a co-substrate, see page 180 under selection and cultivation of L-methionine-producing mutants (i.e. an evolved microorganism). Nakamori et al teach biosynthesis pathway of amino acids and methionine (see title and abstract).

Nakamori et al. also teach limitation of claims 22-32 such limitation of claim 4, defined medium (see page 180 and results) , and limitation of claims

29-32 i.e. E.coli. (see page 180), deletion or modification of a gene (see abstract) , homologous and heterologous gene (see page 182). The prior art anticipates the claimed invention

Status of Claims

9. No claims are allowed.

Conclusion

10. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Khatol Shahnan-Shah whose telephone number is (571)-272-0863.

The examiner can normally be reached on Mondays and Wednesdays from 12:30-6:30 PM and Thursdays from 12:30-4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert B. Mondesi can be reached on 571-272-0956.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Khatol Shahnan-Shah
Art Unit 1645
January 31, 2009

/Robert B Mondesi/
Supervisory Patent Examiner, Art Unit 1645